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Drug Safety Testing Center

Safety Pharmacological Approach for Proarrhythmic Risk Prediction Using IQ-CSRC Drugs (II) - Langendorff Study -

○Koji NAKANO, Fuminori MATSUBARA, Masaru TSUBOI, Kazuhide OKADA, Noriko HASHIGUCHI, Souji MIYAZAKI, Mao YAMAGUCHI, Satomi TOMIZAWA, Rie URA, Taku IZUMI, Hironori OHSHIRO, Hiroshi MATSUKAWA, Akihiro KANNO
Drug Safety Testing Center Co., Ltd., Higashimatsuyama-shi, Saitama, Japan

Introduction

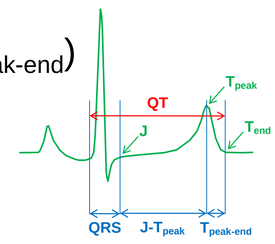
In safety pharmacology studies, it is important to predict the likelihood of proarrhythmic risk. Although *in-silico* models are now available to predict risk of novel drug candidates, there seems to be room for further improvement. As the Langendorff assay can evaluate direct effect of compounds on the heart, it is well known to be useful in arrhythmogenic-risk prediction. In this research on the Langendorff assay, we tested 6 drugs, which had been evaluated in the clinical QT-prolongation assessment by IQ-CSRC. Additionally we performed detailed analysis of the obtained electrocardiogram.

Methods

Langendorff assay, Animals: guinea-pig

Data Collection:

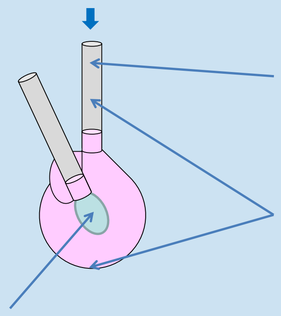
- Electrocardiogram (HR, RR, PR, QRS, QT, QTc, J-T_{peak}c, $T_{peak\text{-}end}$)
- Fridericia's formula: $QTc=QT/RR^{1/3}$
- Left-ventricular Pressure (LVPSP, LVEDP, LV dP/dt max)



Drugs:

- DMSO (vehicle), Flecainide, Verapamil, E-4031
- Ondansetron, Quinine, Dolasetron, Moxifloxacin, Dofetilide, Levocetirizine (6 drugs which were used in the IQ-CSRC study)

The attached heart was perfused with KH solution, and a temperature controller was used to monitor and control the temperature (37.0±0.2ºC). The perfusion pressure was maintained at 70 mmHg.
Each drug was cumulatively applied for 15 minutes per concentration.



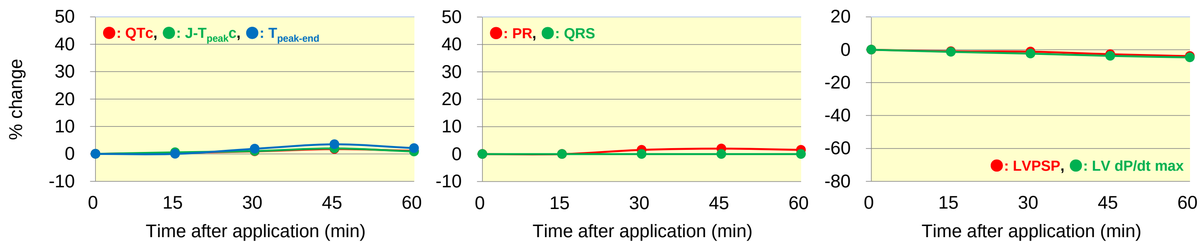
A stainless-steel cannula was inserted in the aorta, followed by attachment to the Langendorff apparatus.

Electrocardiogram electrodes were fixed on the ventricular apex (+), and a stainless-steel cannula was inserted in the aorta (−).
The signals were amplified with an amplifier. The electrocardiogram waveforms were collected and recorded with computer software.

The left-ventricular pressure from the balloon catheter placed in the left ventricle was recorded with a pressure monitor and computer software. Before measurement, the in-balloon pressure was adjusted so that the diastolic blood pressure would be within the range between 0 and 10 mmHg.

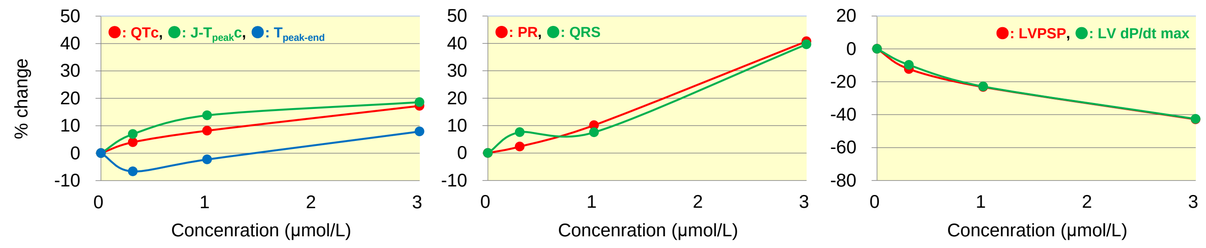
Results

DMSO: Vehicle



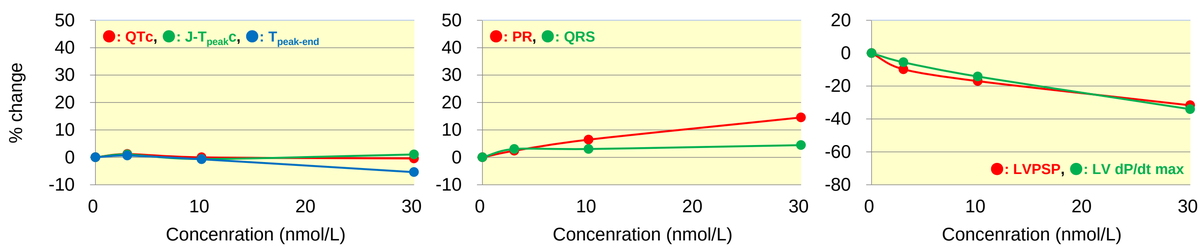
No effect

Flecainide: Sodium channel blocker



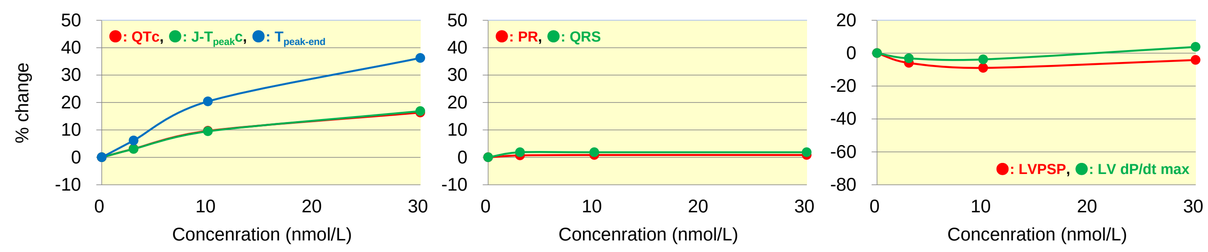
Prolongation of the QRS duration and QTc and J-T_{peak}c intervals and deterioration of the cardiac function

Verapamil: Calcium channel blocker



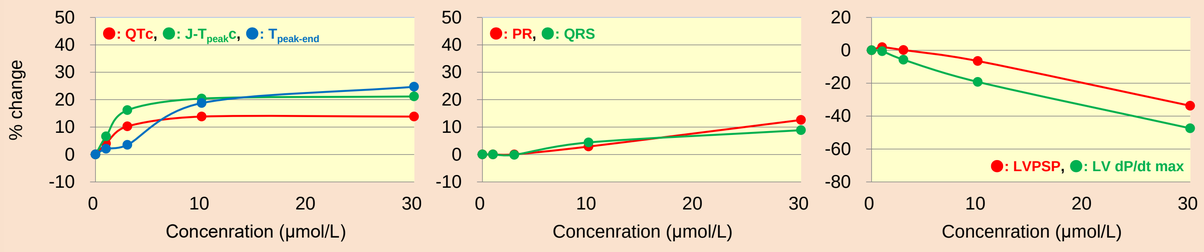
Deterioration of the cardiac function

E-4031: Potassium channel blocker



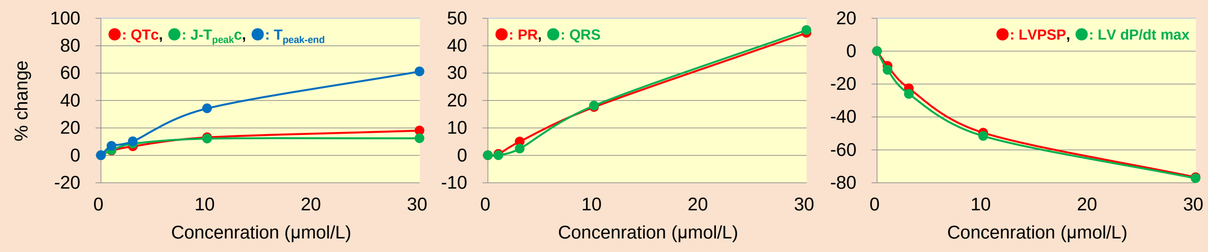
Prolongation of the QTc, J-T_{peak}c, and $T_{peak\text{-}end}$ intervals

Ondansetron: $I_K > I_{Na}, I_{Ca}$



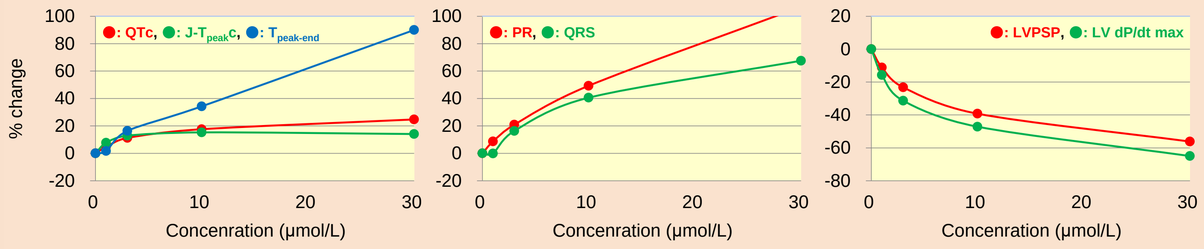
Prolongation of the QTc, J-T_{peak}c, and $T_{peak\text{-}end}$ intervals and deterioration of the cardiac function

Quinine: Multichannel blocking



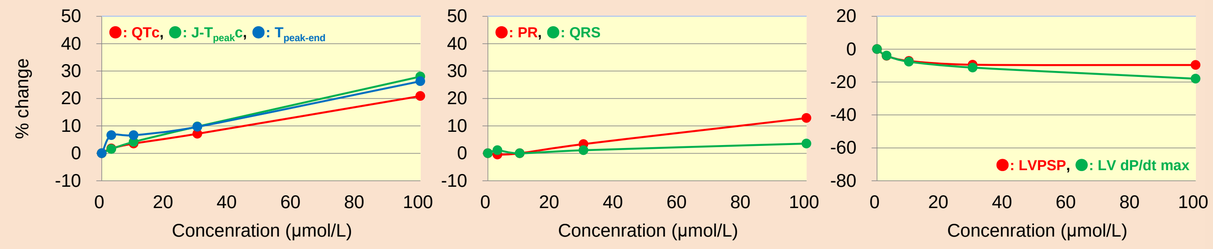
Prolongation of the QRS duration and QTc, J-T_{peak}c, and $T_{peak\text{-}end}$ intervals and deterioration of the cardiac function

Dolasetron: Multichannel blocking



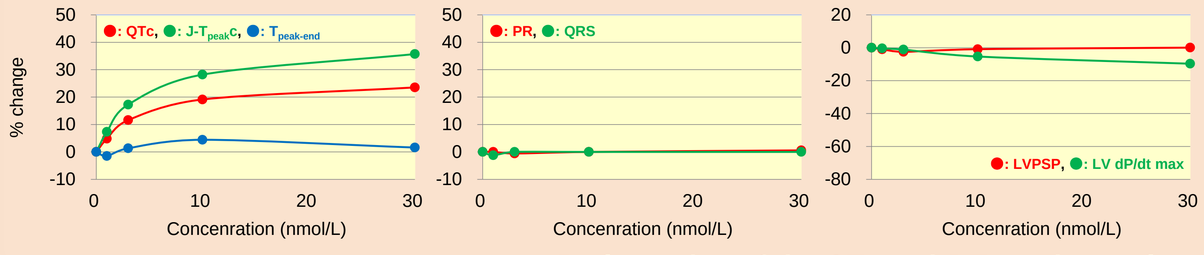
Prolongation of the QRS duration and QTc, J-T_{peak}c, and $T_{peak\text{-}end}$ intervals and deterioration of the cardiac function

Moxifloxacin: $I_K >> I_{Ca} > I_{Na}$



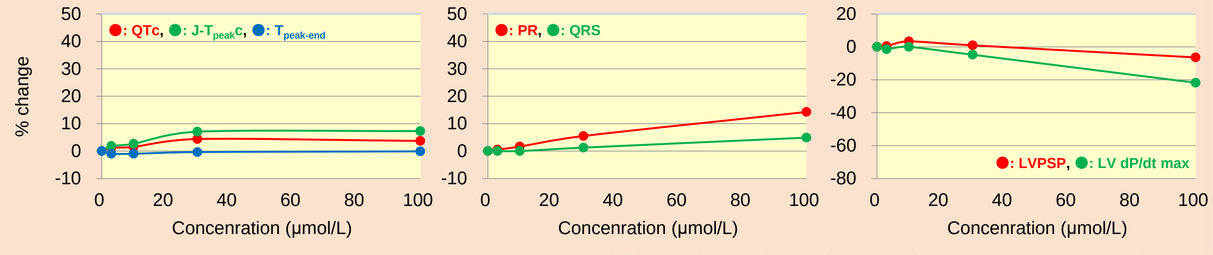
Prolongation of the QTc, J-T_{peak}c, and $T_{peak\text{-}end}$ intervals

Dofetilide: I_K inhibition



Prolongation of the QTc and J-T_{peak}c intervals

Levocetirizine



Slight deterioration of the cardiac function

Conclusion

The results indicate that more-sophisticated risk prediction is possible by assessing multiple parameters with the Langendorff assay.